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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/635,908	08/07/2003	Reinier Lh Bolhuis	2923-552	7844
6449 7590 02/26/2007 ROTHWELL, FIGG, ERNST & MANBECK, P.C. 1425 K STREET, N.W. SUITE 800 WASHINGTON, DC 20005			EXAMINER TUNGATURTHI, PARITHOSH K	
			ART UNIT 1643	PAPER NUMBER
SHORTENED STATUTORY PERIOD OF RESPONSE		NOTIFICATION DATE	DELIVERY MODE	
3 MONTHS		02/26/2007	ELECTRONIC	

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 02/26/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

## Office Action Summary

Application No.

10/635,908

Applicant(s)

BOLHUIS ET AL.

Examiner

Parithosh K. Tungaturthi

Art Unit

1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 20 December 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-11 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_.

### **DETAILED ACTION**

1. The applicant has timely traversed the non-final rejection in the reply filed on 12/20/2006, and a response to the arguments is set forth.
2. Claims 1-4 and 6 have been amended.
3. Claim 11 has been newly added.
4. Claims 1-11 are under examination.
5. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior office action.

### ***Rejections Withdrawn***

6. The rejection of claims 1-10 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claims.
7. The rejection of claims 1-10 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant vector system comprising a nucleic acid encoding the antigen-binding site, wherein the antigen is G250....., does not reasonably provide enablement for a recombinant vector system comprising at least one copy of a nucleic acid ..... heavy chain is withdrawn in view of amendments to the claims.

Art Unit: 1643

8. The rejection of claims 1-5 under 35 U.S.C. 102(b) as being anticipated by Weijtens et al (The Journal of Immunology, 157:836-843, 1996) as evidenced by the specification is withdrawn in view of amendments to the claims.

9. The rejection of claims 1-5 under 35 U.S.C. 102(b) as being anticipated by Carceller et al (U.S. Patent 5969107, Date Issued: October 19<sup>th</sup>, 1999) is withdrawn in view of amendments to the claims.

***Rejections Maintained***

10. Claims 1-10 remain rejected and the newly added claim 11 is further rejected under 35 U.S.C. 103(a) as being unpatentable over Oosterwijk et al (a) (WO 88/08854, Published 11/17/1988) as evidenced by the specification in view of Oosterwijk et al (b) (Seminars in Oncology. 1995. 22(1): 34-41) in view of Robinson et al (U.S. Patent 5,618,920; Issued 4/8/1997) and in view of Queen et al (U.S. Patent 5,530,101; Issued 6/25/1996).

The applicants argue that there is no guidance in the prior art leading one to the actual sequences.....the prior art provides at best a possibility that one might be able to figure out the sequences if one wished so, but still leaves one completely in the dark as to what the actual sequences are....the mere knowledge of the existence of monoclonal G250 antibody or a hybridoma cell producing the antibody does not impart knowledge of

Art Unit: 1643

how to obtain the antibody or the hybridoma cell (page 10 of the response filed on 12/20/2006).

In response to the above arguments, the applicant is reminded of the art cited in the previous office action; particularly Robinson et al who teach the determination of nucleic acids encoding VH and VL of any known antibody and use of said VH and VL to produce FV. Robinson et al also teach the production of consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity. Thus, from the teachings of Robinson et al and Ward et al, one of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have obtained the nucleic acids of VH and VL from a known hybridoma.

Oosterwijk et al (a) teach the hybridoma which produces monoclonal antibody G250 and that it can be used as a therapeutic agent or that the antibody can be humanized further couple it with a diagnostic marker or a cytotoxic agent. Thus, one of ordinary skill in the art would be motivated to use the hybridoma producing the monoclonal G250 antibody as taught by Oosterwijk et al and determine the nucleic acid sequences from the procedures as taught by Robinson et al.

Further, in regard to the newly added claim, claim 11, wherein the diagnostic marker is a radioactive marker; Oosterwijk et al teach that the antibody as described can be coupled with preferred radioisotope (see page 11, in particular).

Thus, based on the teachings of Robinson et al and Oosterwijk et al, the art recognizes that there was a reasonable expectation of success that the nucleic acid sequence of the VH and VL of the art known G250 antibody could be established from the G250 hybridoma, and hence the invention as claimed is obvious to one of ordinary skill in the art at the time the invention was made.

***New Grounds of Rejection and Response to Arguments***

11. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weijtens et al (The Journal of Immunology, 157:836-843, 1996) as evidenced by the specification in view of Oosterwijk et al (b) (Seminars in Oncology, 1995, 22(1): 34-41) in view of Orlandi et al (Proc. Natl. Acad. Sci. USA, 86:3833-3837, 1989) in view of Cabilly et al (U.S Patent 4816567, Issued 3/89) in view of Robinson et al (U.S. Patent 5618920, Filed 4/94) in view of Huston et al (U.S. Patent 5258498, Issued 11/93) and in view of Queen et al (U.S. Patent 5,530,101; Issued 6/25/1996).

Claims 1-5 and 10 are interpreted as being drawn to the nucleic acid sequence of the monoclonal antibody G250 and antibody fragments and the method of production of such antibody or antibody fragments. In addition, claims 6-9 and 11 are interpreted as said method wherein the antibody is humanized, wherein the antibody can be used as a diagnostic or therapeutic agent, coupled with a diagnostic marker, cytotoxic agent.

Weijtens et al teach lymphocytes that express a single-chain Fv receptor; wherein the genes encoding the VH and VL of the G250 monoclonal antibody were isolated from cDNA prepared from the G250 hybridoma producing cells and fused to the Fc( $\epsilon$ )RI signaling receptor  $\gamma$ -chain of mast cells, introduced into a vector and expressed in lymphocytes (see entire document, particularly page 837 and page 836, right column). Thus, the lymphocytes expressing the scFv are eukaryotic cells derived from hybridoma cell DSM ACC 2526 obtained by transfer of the genetic material encoding the antigen-binding site (i.e., VH and VL) of the G250 antibody into the lymphocytes (i.e., receptor cell or cell derived from hybridoma DSM ACC 2526) which produce a single-chain antibody (i.e., scFv).

Oosterwijk et al (b) teach the Use of Monoclonal Antibody G250 in the Therapy of Renal-Cell Carcinoma.

Orlandi et al teach a general method for obtaining the VH and the VL genes and the amino acid sequence of an antibody by PCR from the hybridoma cell. Orlandi also teaches primers and the use of said primers to clone DNA encoding murine variable heavy regions (see page 3833 and 3834) and the method obtained the sequences for five of the hybridomas for which it was applied.

Robinson et al (see columns 12-22) teach Fv derived from a known antibody. Robinson et al teach Fv, determination of nucleic acids encoding VH and VL of any known antibody and use of said VH and VL to produce FV (see column 1-45, and columns 12-22). Robinson et al teach that "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization

and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph).

Cabilly et al teach that regarding VH and VL nucleic acid sequences that, "the variable regions can conveniently be derived from presently known sources using readily available hybridomas" (see column 6, last paragraph)

Huston et al teach that the sequence of the VH and VL of a known antibody can be determined by amino acid sequencing and "The 5' end portion of the mRNA can be used to produce the cDNA for subsequent sequencing or the amino acid sequence of the hypervariable and flanking framework regions can be determined by amino acid sequencing of the V regions of the H and L chains. Such sequence analysis is now conducted routinely".

Queen et al teach human antibodies and humanized antibodies comprising CDRs from non-human donor VH and VL chains, human framework and constant regions and the humanized antibody binds the same antigen as the non-human donor antibody, providing the CDRs (see column 2-3 and 12-16, in particular). Queen et al teach humanized antibodies and antigen-binding fragments thereof (i.e. single-chain antibodies) that are less immunogenic in human patients compared to mouse antibodies and thus, better suited for human therapy as well as vectors and host cells for expressing and producing the humanized antibodies including E.coli, yeast cells, myeloma cells and CHO-cells (see entire document, particularly column 2, columns 11, lines 18-34 and columns 16-18 and Examples). Queen et al also teach antibody conjugation to a variety of cytotoxic agents including radioisotopes, chemotherapeutic

Art Unit: 1643

drugs, toxins and the antibodies may be labeled or unlabeled for diagnostic purposes (see column 20, lines 1-33).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the methods taught by Orlandi et al, Cabilly et al, Robinson et al and Huston et al to obtain the nucleic acids encoding the VH and VL from the G250 hybridoma taught by Weijtens et al to produce the claimed nucleic acid sequence, and further humanize it as taught by Queen et al.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success at the time the invention was made to have used the teachings of Weijtens et al because Weijtens et al teach the antibody G250, the same antibody as the claimed in the instant claims and also the hybridoma which produces monoclonal antibody G250.

Although Weijtens et al do not teach the nucleotide sequences of heavy and light chain CDRs of the antibody as claimed, the references cited in this rejection teach FV, nucleic acids encoding VH and VL and the methods of making FV based on the nucleic acid sequence of any known antibody VH and VL, and methods of determining the nucleic acid sequence of any known antibody VH and VL. All Fvs are structurally similar in that they contain similar numbers of amino acids organized in a similar fashion (e.g. they contain a VH and VL wherein the VH and VL contain framework and variable region amino acids). Thus it would not have been undue experimentation to obtain the

Art Unit: 1643

nucleic acid sequence as claimed because the art recognizes that hundreds, if not thousands of antibody molecule VH and VL regions have been cloned and sequenced. As taught by Orlandi et al it was routine to obtain the VH and the VL genes from PCR primers from the hybridoma of an antibody and "our primers might amplify most immunoglobulin mRNA of the mouse repertoire" (see page 3836, right column) and "the teachings should lead to the cloning of antigen-binding specificities directly from immunoglobulin genes" (see abstract, last sentence). Cabilly et al teach that regarding VH and VL nucleic acid sequences that, "the variable regions can conveniently be derived from presently known sources using readily available hybridomas" (see column 6, last paragraph). Robinson et al teach, "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph). Huston et al teach "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph). Thus, the art recognized that there was a reasonable expectation of success that the nucleic acid sequence of the CDRs of heavy and light chains of the art known as G250 antibody could be established using techniques disclosed in the references used in the instant rejection. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibody with the antibody of Weijtens et al, the burden of proof is upon the Applicants to show an unobvious distinction between the

Art Unit: 1643

structural and functional characteristics of the claimed antibody and the antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to apply the methods of Orlandi et al, Cabilly et al, Robinson et al and Huston et al to obtain the nucleic acids encoding the VH and VL of G250 monoclonal antibody taught by Weijtens et al and produce cells (i.e. host cells) including E.coli, yeast cells, myeloma cells and CHO-cells nucleic acids encoding humanized G250 antibodies and antigen-binding fragments thereof for therapy in renal cell carcinoma patients as taught by Osoterwijk et al (b) because humanized antibodies are less immunogenic in human patients compared to mouse antibodies and better suited for human therapy according to Queen et al who also teach antibody conjugation to a variety of agents.

Thus, it would have been further prima facie obvious to one of ordinary skill in the art at the time the invention was made to have obtained the nucleic acids encoding the VH and VL from the G250 hybridoma, wherein the monoclonal antibody G250 can be used in the therapy of Renal-Cell Carcinoma patients in view of Weijtens et al as evidenced by the specification and Orlandi et al, Cabilly et al, Robinson et al, Huston et al, Queen et al and Osoterwijk et al (b).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Response to Arguments

The applicants argue that Weijtens does not disclose any sequence information of G250 or how to make the hybridoma cell which produces G250 monoclonal antibodies ... and that it is highly unlikely that a hybridoma cell producing the G250 antibody would be consistently or repeatedly obtainable ... using prior art procedures (pages 7-9 of the response filed on 12/20/2006).

As stated by the applicant (page 8 of the response filed on 12/20/2006), Weijtens et al teach that the genes encoding VH and VL of the G250 monoclonal antibody were isolated from cDNA prepared from the G250 hybridoma producing cells. Thus, Weijtens et al teach the antibody G250, the same antibody as the claimed in the instant claims, that bind to the same antigen as disclosed in the specification. Thus, it can be concluded that Weijtens et al have determined the nucleic acid sequences encoding the Vh and Vl of antibodies that are directed to the same antigen that the claimed antibodies bind, which would reasonably convey one skill in the art that Weijtens et al's antibody also possesses the same structural and functional properties as those of the antibodies claimed.

Thus, it is the examiners position that Weijtens et al anticipate the claimed invention.

Further, the applicant argues that the antigen recognized by the G250 antibody is not a linear epitope which can be specified by a defined amino acid.....it is evident from these data that the identification and isolation of the specific G250 epitope is

exceedingly complicated due to the fact that .....Weijtens is not an anticipatory reference (page 9 of the remarks filed on 12/20/2006).

In response to the above arguments, the applicant is reminded that the claims are drawn to a recombinant vector system encoding for G250 antibody and a method for recombinant production of such antibody. The claims are not drawn to any specific characteristics of the G250 antibody that differentiates the claimed invention from the prior art cited. The U.S. Application cited by the applicant describes the mapping of the epitope recognized by the monoclonal G250 antibody, however the correlation of such citation with the claimed invention is not understood and the applicant is requested to clearly point out the relevance of such arguments. In addition, the claims as written are not drawn to any structural conformation of the antigen for the antibody to bind, and hence the above-mentioned arguments are not found pertinent.

In addition, the argument that the immunogen of Oosterwijk comprises of multitude of antigenic determinants or epitopes which are capable of eliciting immune reaction (page 8 of the response filed on 12/20/2006) is not relevant; because the antibody disclosed in the prior art is G250 monoclonal antibody and the antibody claimed is G250 monoclonal antibody that binds to the same antigen as described in the prior art.

### ***Conclusion***

12. No claims are allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

15. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,  
Parithosh K. Tungaturthi Ph.D.  
(571) 272-8789

  
SHEELA HUFF  
PRIMARY EXAMINER